

## **REMARKS**

### **Introduction**

Receipt is acknowledged of an Advisory Action dated June 15, 2004. In the Advisory Action, the Examiner refused to enter the amendment and maintained the rejection of claims 32, 35, 36, 41, and 44 as allegedly indefinite, not enabled and obvious as maintained in the final rejection of January 28, 2004. Applicants respectfully traverse these rejections and the rejections set forth in the final rejection and have amended claims 32 and 44 to recite, as suggested by the Examiner in the Advisory Action, that the neoplastic or tumor cells are “freshly isolated” from patient tissue, and can be a primary tumor cell. Support for this amendment can be found in the specification on page 19, lines 10 – 17 and page 24, lines 25-29. Additionally, these claims now recite that the purification step is accomplished “in less than about 24 to 48 hours” after exposure to the fusion conditions. Support for this language can be found in the specification on page 8, lines 3-5. Both of these features support applicants’ position that the prepare hybrid cell population is prepared in a relatively short period of time from the receipt of the patient’s tumor to the resultant hybrid cell population.

The new dependent claims are supported by the previous dependent claims and pages 8 and 9 of the specification which discloses characteristics of the dyes.

### **Status of the Claims**

In this response applicants amended claims 32, 35, 36, and 44 and added new claims 45 - 53. Support for the revised claims can be found throughout the specification. Upon entry of this amendment, claims 32, 35, 36, 41, and 44 -53 will be under examination.

### **35 USC § 112, first paragraph**

In the action, the examiner rejected claims 32, 35, 36, 41, and 44 allegedly for nonenablement. Specifically, the examiner indicated that “the experimental data confirm the preservation of tumor antigen diversity, but not other diversity” (office action at 3). Thus, in the interest of expediting prosecution, applicants amended claims 32 and 44 to recite the

preservation of tumor antigen diversity. Applicants submit that this amendment addresses the examiner's concerns regarding the word "diversity" and request withdrawal of the rejection.

**35 USC § 112, second paragraph**

Furthermore, the examiner rejected claims 32, 35, 36, 41, and 44 allegedly for indefiniteness, asserting that "the claims have not been made clear [as to] what type of diversity they refer to" (office action at 4). As discussed above, the presently claimed invention recites "tumor antigen diversity," thereby rendering the instant rejection moot.

**35 USC § 103**

Continuing, the examiner rejected all pending claims as allegedly obvious over Gong, in view of Koolwijk. In particular, the examiner stated "the motivation to combine the references is not relied on preserving diversity but the efficacy of the process" (office action at 7). In other words, the examiner cites Koolwijk and asserts that "saving time and cost has always been the motivation for improvement in the advance of all fields of technology" (office action at 7).

However, the method described in Koolwijk comprises using a Percoll density gradient centrifugation, followed by fluorescence-activated cell sorting. Not only does Koolwijk describe a selection process for hybrid-hybridomas, *i.e.*, cells that are not dendritic cell fusions, but Koolwijk describes the Percoll gradient step as critical to achieving high yields ("by using Percoll density gradient centrifugation before sorting, the overall increase of producing hybrid hybridomas was approximately 8 fold" (Koolwijk at 223)). Thus, a skilled artisan would not take the teachings of Gong and look to a two-step Koolwijk approach for a faster and cheaper method of selection.

In response to the Examiner's assessment of the relative simplicity of the Percoll gradient centrifugation procedure, Applicants' arguments address the Examiner's original rationale for combining Gong and Koolwijk as merely substituting one step for another. Although the Examiner asserts that the Percoll gradient is a relatively simple and short procedure, Applicants submit that a two step process requires additional manipulation of the

cells as compared to simply culturing the cells in a selective media as taught by Gong. Furthermore, to the extent that the Examiner's statement that "saving time and cost has always been the motivation for improvement in the advance of all fields of technology" suggests that cost savings would be a motivation to use Koolwijk's method to modify Gong, applicants respectfully disagree. As the Examiner is no doubt aware, the equipment needed to run FACS requires a major capital investment. In view of this capital expense, especially as compared to the cost of routine cell culturing, applicants respectfully suggest that the Koolwijk method would be more costly than the culture selection method described in Gong.

Furthermore, at the time of filing, dendritic cell and other cell fusions were usually selected by metabolic selection, not by FACS. Therefore, one of skill in the art would not look to substitute a more "experimental" approach for cell fusion selection when other more common prior art methods such as antibody and metabolic selection that do not appear to pose any difficulties were available.

Lastly, Gong describes success in treating cancer with dendritic cell fusions and therefore, one of skill in the art would not look to Koolwijk or another reference to improve upon the method in Gong. Indeed, the teachings in Gong would not indicate that another method for selecting cells would be more effective in identifying cell fusions suitable for cancer treatment. In fact, a skilled artisan would not be motivated to modify Gong since Gong described how well his cell fusions worked. But Gong and others failed to recognize the significance of preserving antigen diversity in the dendritic cell fusions. As previously argued, while a skilled artisan knows that culturing cells over a period of time results in loss of tumor antigen diversity, the significance of this effect was not appreciated at the time of filing the present application. Thus, one would not be motivated to change the method of Gong to avoid culturing cells because the import of not culturing cells was not recognized prior to the present invention.

In view of the foregoing arguments, it is respectfully requested that the present rejections be withdrawn.

**CONCLUSION**

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and arguments is kindly requested.

It is respectfully urged that the present application is now in condition for allowance. Early notice to that effect is earnestly solicited.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application

Respectfully submitted,

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